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Investigation of the relationship between sleep duration, all-cause mortality, and preexisting disease

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Investigation of the relationship between sleep duration, all-cause mortality, and preexisting disease

Abstract

Objective: To examine the relationship between sleep duration and mortality and to quantify the likely impact of residual confounding due to poor health status on any observed association. **Methods:** The sample included 227,815 Australian adults aged 45 years and older recruited from 2006–2009 (the 45 and Up Study). Sleep duration and relevant covariates (e.g., health status, demographic factors) were assessed through a self-report questionnaire. These data were linked with mortality data from the New South Wales Registry of Births, Deaths, and Marriages up to December 2010 (mean follow-up period, 2.8 y). Cox proportional hazards models examined the relationship between sleep duration and all-cause mortality adjusting for relevant sociodemographic covariates (e.g., age, gender, marital status), with further stratification by baseline health status based on physical functioning and preexisting disease. **Results:** The adjusted mortality risk was significantly higher in individuals reporting (hazard ratio [HR], 1.13[1.01–1.25]) and ≥ 10 hours of sleep (HR, 1.26[1.16–1.36]), compared to those reporting 7 hours of sleep per night. These associations differed by baseline health status ($p[\text{interaction}] = 0.026$) such that there was no significant relationship of sleep duration to mortality in those with good health at baseline. **Conclusion:** Following careful prospective controlling for baseline health, mortality risk does not significantly vary according to sleep duration. Previous findings suggesting a relationship between sleep duration and mortality could be affected by residual confounding by poor preexisting health, as reflected by a combination of preexisting illnesses and functional limitations.

Keywords

preexisting, mortality, cause, duration, disease, investigation, all, relationship, between, sleep

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INVESTIGATION OF THE RELATIONSHIP BETWEEN SLEEP DURATION, ALL-CAUSE MORTALITY AND PRE-EXISTING DISEASE

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ABSTRACT

Objective: To examine the relationship between sleep duration and mortality and to quantify the likely impact of residual confounding due to poor health status on any observed association.

Methods: The sample included 227,815 Australian adults aged 45 years and older recruited from 2006–2009 (the 45 and Up Study). Sleep duration and relevant covariates (e.g., health status, demographic factors) were assessed through a self-report questionnaire. These data were linked with mortality data from the New South Wales Registry of Births, Deaths, and Marriages up to December 2010 (mean follow-up period, 2.8 y). Cox proportional hazards models examined the relationship between sleep duration and all-cause mortality adjusting for relevant sociodemographic covariates (e.g., age, gender, marital status), with further stratification by baseline health status based on physical functioning and preexisting disease.

Results: The adjusted mortality risk was significantly higher in individuals reporting <6 hours of sleep (hazard ratio [HR], 1.13[1.01–1.25]) and ≥ 10 hours of sleep (HR, 1.26[1.16–1.36]), compared to those reporting 7 hours of sleep per night. These associations differed by baseline health status (p [interaction] = 0.026) such that there was no significant relationship of sleep duration to mortality in those with good health at baseline.

Conclusion: Following careful prospective controlling for baseline health, mortality risk does not significantly vary according to sleep duration. Previous findings suggesting a relationship between sleep duration and mortality could be affected by residual confounding by poor preexisting health, as reflected by a combination of preexisting illnesses and functional limitations.

Keywords: sleep duration, mortality, pre-existing disease, residual confounding, health status, prospective.

INTRODUCTION

A growing body of research indicates a U-shaped association between sleep duration and mortality risk. In particular large-scale epidemiological studies indicate that individuals who report short (e.g., ≤ 6 hours a night) and long sleep (e.g., ≥ 9 hours a night) durations have elevated odds of mortality relative to those sleeping 7 – 8 hours a night [1-12]. A number of mechanisms have been proposed to explain this relationship. For instance, it has been suggested that short sleep could contribute to mortality via chronic health conditions (e.g., heart disease and diabetes) and/or by increasing the likelihood of accidents because of impaired cognitive functioning.

Despite causal mechanisms that have been proposed linking long sleep to mortality, a number of studies have suggested that this association likely reflects residual confounding with underlying poor health [13], and the relationship of short sleep to mortality may be similarly affected. However, detailed empirical data on this are limited. Hence, rather than sleep duration independently contributing to mortality risk, it is possible that individuals with preexisting health conditions experience disturbed sleep patterns with these preexisting conditions themselves contributing to greater mortality [1] and [14]. Preexisting health conditions have been shown to underlie the relationships between sleep disturbances and other health outcomes. For instance, Cairns et al. [15] found that the apparent association between daytime napping and subsequent cancer risk was the result of underlying disease, rather than napping itself contributing to cancer risk.

Few studies have examined the impact of preexisting health conditions on the association between sleep and mortality, and those that are available have produced mixed results. Patel et al. [7], Suzuki et al. [10], and Kakizaki et al. [16] found that short sleep was linked with

elevated mortality in both healthy and less healthy individuals. In contrast, using a wider variety of health-related measures, Mesas et al. [1] only observed the association between short sleep and mortality in those with poorer cognitive function. The findings for long sleep have been more consistent, with long sleep generally associated with mortality risk regardless of health status [1], [7], [8], [10] and [16]. However, Kakizaki et al. [16] did find that the relationship between long sleep and stroke mortality was higher in those with poorer health, as reflected by self-rated health and physical function.

In our paper, we aimed to prospectively investigate the relationship between sleep duration and mortality. This investigation involved examining the extent to which any observed variation in these relationships could be explained by baseline health status. We assessed health status in relation to preexisting health conditions (e.g., cancer, heart disease) and physical functional limitation; in combination, these factors provide a more comprehensive measure of baseline health compared to some previous studies, and they allow for an examination of the severity of poor health. We hypothesized, a priori, that if sleep duration were to independently and causally influence mortality as suggested by previous research, then an association between sleep duration and mortality would be evident in individuals who were healthy and less healthy at baseline, provided appropriate statistical power is present. If this association is absent in individuals in adequate health at baseline and is only present in individuals with preexisting disease or functional limitation, this finding would suggest that there is residual confounding with poor baseline health in the association between sleep duration and mortality risk.

METHODS

Our paper utilized data collected through the 45 and Up Study, a large cohort study of 267,153 adults ages 45 years and older who resided in the state of New South Wales in Australia. The primary objective of the 45 and Up Study is to collect information from a large heterogeneous sample of adults to investigate healthy aging [17]. Participants for this study were recruited through the Medicare Australia enrollment database, which is the publicly funded health insurance system in Australia and includes virtually all Australian residents. Potential participants were mailed a self-report questionnaire assessing a variety of sociodemographic and health-related factors; the response rate was approximately 18%. Informed consent was obtained from all participants and the 45 and Up Study received ethics approval from the University of New South Wales Human Research Ethics Committee. Ethics approval to use the 45 and Up Study data in our paper was obtained from the New South Wales Population and Health Services Ethics Committee.

Measures

Data on all variables assessed in this study besides the index of remoteness and mortality were derived the baseline 45 and Up Study questionnaire. The self-report questionnaire asked the following question on sleep duration, “About how many hours in each 24-hour day do you usually spend sleeping (including at night and naps)?” Sleep duration was reported on a continuous scale and then divided into 6 categories: < 6 hours sleep, 6 hours sleep (i.e., ≥ 6 hours and < 7 hours), 7 hours (i.e., ≥ 7 hours and < 8 hours), 8 hours (i.e., ≥ 8 hours and < 9 hours), 9 hours (i.e., ≥ 9 hours and < 10 hours), and ≥ 10 hours [9]. The reference category was defined, a priori, as 7 hours in a 24-hour period, which is consistent with previous research [9]. Data on all-cause mortality between February 1, 2006 and December 31, 2010 were available from the New South Wales Registry of Births, Deaths and Marriages and were linked through the Centre for Health Record Linkage (CHeReL: NSW, Australia). The mean period of follow-up was 2.8 years.

Health status was determined on the basis of preexisting illness at baseline and functional capacity. The presence of preexisting illness was based on self-reported doctor diagnosis of diabetes mellitus, heart disease, or stroke, as well as melanoma, breast cancer (in women), prostate cancer (in men), and other cancers. These conditions were chosen to be as consistent as possible with the Charlson comorbidity index scale [18] using the available data. There were complete data for all comorbid preexisting illnesses (e.g., diabetes mellitus, heart disease, stroke, melanoma, breast cancer [in women], prostate cancer [in men], other cancers), but we excluded a small number of individuals who had undergone treatment for cancer in the month prior to the survey ($n = 6708$).

Functional capacity was assessed using the 10-item physical functioning subscale of the Medical Outcomes Study; this subscale is equivalent to the physical functioning subscale of the short-form health survey 36 [19]. Higher scores on this scale indicate fewer functional limitations. On the basis of preexisting illness and functional capacity we created 2 groups: (1) healthy, whereby individuals had no reported disease at baseline and a physical functioning score of 75 to 100 and (2) less healthy, defined as having one or more chronic conditions at baseline or a physical functioning score of less than 75. There were some missing data on responses to the physical functioning items; for participants with less than 50% of missing data on these items, imputation based on the mean of other values was used [20]. However, when more than 50% of items were missing, the Medical Outcomes Study physical functioning scale variable was treated as missing ($N = 21,364$); for these individuals health status was assigned by preexisting serious illness. We note that this did not bias the reported results, as a sensitivity analysis that excluded these 21,364 individuals produced highly concordant results as those reported with unchanged conclusions.

A number of covariates were included in the analyses. These included gender, age (divided into 5-year age groups), education level (no school certificate or other qualification, school of intermediate certificate, higher school or leaving certificate, trade/diploma/certificate, and University degree or higher), and marital status (single, widowed, divorced or separated, married or de facto relationship). In addition, participants were asked about their health insurance status (no private health insurance, private health insurance, or Department of Veterans' Affairs card), and their yearly household income (in Australian dollars) before tax (< \$10 000, \$10 000-\$29 999, \$30 000-\$69 999, > \$70 000, with "I would rather not answer the question" as a further response category). Information on weekly alcohol consumption (0 drinks, 1 – 7 drinks, 8 – 14 drinks, ≥ 15 drinks), physical activity (≤ 30 min/d, > 30 min/d), and smoking status (current smoker, former smoker, never smoker) were also collected, as were self-reported height and weight which were used to calculate body mass index (≤ 18.5 kg/m², 18.5 -<25.0 kg/m², 25.0-29.9 kg/m², ≥ 30.0 kg/m²).

Participant postcodes derived from the Medicare Australia enrollment database were used to assess remoteness (i.e., if individuals lived in a major city, rural, or remote area). This process was achieved using the Accessibility/Remoteness Index of Australia (ARIA) [21], in which participants were categorized as living in a major city (ARIA, 0–0.2), an inner regional area (ARIA > 0.2 and ≤ 2.4), an outer regional area (ARIA > 2.4 and ≤ 5.92), or a remote/very remote area (ARIA > 5.92). Participants with missing data for sleep duration, age, or gender (n=7426) were excluded from the analyses. For the remaining variables, an additional category was created to code missing data where appropriate.

Statistical Analysis

The association between sleep duration and all-cause mortality was examined using Cox proportional hazards models, with time to death from date of baseline questionnaire

specified as the outcome. Individuals surviving the follow-up period were treated as censored observations. All models satisfied the Cox proportional hazards model assumption. The analyses were performed using Stata version 11.1, with the relative risk for death estimated for each sleep category relative to the reference category expressed as a hazard ratio (HR), with 95% confidence intervals (CI). The analyses involved testing an initial model, in which we examined the relationship between sleep duration and mortality, controlling for age and gender. A second model was then tested whereby we entered additional covariates into the analysis. For parsimony, covariates that did not explain variation in all-cause mortality at $p < 0.05$ were removed from the final multivariate model.

We examined the main association between sleep duration and mortality separately for individuals defined as healthy and less healthy. An interaction term examining if the relationship between sleep duration and mortality varied according to health status was then added to the model. This interaction term was formed as a multiplicative combination of the categorical sleep duration predictor with 6 categories (one of which [7 h] was the reference category) and the binary health status covariate with 2 categories (one of which [healthy] was the reference category). The significance of the interaction term was examined using a likelihood ratio test, which compared the model with and without the interaction terms. Investigation of a significant interaction effect was separately performed for the healthy and less healthy groups. Statistical significance was determined by a p value of <0.05 .

RESULTS

Linked data were available for 241,949 adults; however, the final sample consisted of 227,815 participants (53.7% women, 46.3% men) aged 45 years and older at baseline when cases with missing data (e.g., sleep duration, age, gender) were excluded. Most participants were aged 45 to 64 years at baseline (60.7%). Consistent with cohorts from other countries, the majority of our sample reported sleep durations of 7 hours (23.9%) or 8 hours (40.7%) a night. As shown in Table 1, 15.8% reported short sleep (i.e., ≤ 6 hours a night) with 19.6% reporting long sleep duration (i.e., ≥ 9 hours). Females and individuals aged ≥ 80 years were significantly more likely to report short sleep, whereas long sleep was more likely to be reported by males and those aged ≥ 80 years. Baseline health status was also significantly associated with sleep duration. In particular, there was evidence of a U-shaped association between pre-existing illness and sleep duration, as well as between physical functioning and sleep duration.

Table 1. The relationship between sleep duration and key study variables.

	<6 h (n = 8308; 3.6%)	6 h (n = 27,797; 12.2%)	7 h (n = 54,336; 23.9%)	8 h (n = 97,791; 40.7%)	9 h (n = 27,111; 11.9%)	P 10 h (n = 17,472; 7.7%)	p Value
Gender							<0.001
Women	4905 (4.0%)	15,223 (12.5%)	28,626 (23.4%)	50,821 (41.6%)	14,392 (11.8%)	8170 (6.7%)	
Men	3403 (3.2%)	12,574 (11.9%)	25,710 (24.3%)	41,970 (39.7%)	12,719 (12.0%)	9302 (8.8%)	
Age							<0.001
45–64 y	4426 (3.2%)	17,852 (12.8%)	37,936 (27.2%)	58,751 (42.1%)	13,943 (10.0%)	6650 (4.8%)	
65–79 y	2538 (3.9%)	7359 (11.3%)	12,863 (19.7%)	26,182 (40.1%)	9639 (14.8%)	6637 (10.2%)	
P 80 y	1344 (5.8%)	2586 (11.2%)	3537 (15.4%)	7858 (34.1%)	3529 (15.3%)	4185 (18.2%)	
Preexisting illnesses							
None	5855 (3.3%)	21,460 (12.2%)	44,188 (25.2%)	72,945 (41.6%)	19,952 (11.4%)	10,806 (6.2%)	<0.001
P 1	2453 (4.7%)	6337 (12.0%)	10,148 (19.3%)	19,846 (37.7%)	7159 (13.6%)	6666 (12.7%)	
MOS-PF							<0.001
<75	2873 (6.4%)	5832 (13.0%)	7371 (16.4%)	15,117 (33.7%)	6144 (13.7%)	7570 (16.9%)	

	<6 h (n = 8308; 3.6%)	6 h (n = 27,797; 12.2%)	7 h (n = 54,336; 23.9%)	8 h (n = 97,791; 40.7%)	9 h (n = 27,111; 11.9%)	P 10 h (n = 17,472; 7.7%)	p Value
75–100	5435 (3.0%)	21,965 (12.0%)	46,965 (25.7%)	77,674 (42.5%)	20,967 (11.5%)	9902 (5.4%)	

Abbreviations: h, hour; y, year; MOS-PF, Medical Outcomes Study-Physical Functioning Scale.

Over the 5-year period, there was a total of 8782 deaths from all causes. After adjusting for age and gender, the risk for mortality during the follow-up period was significantly higher in individuals reporting short or long sleep duration compared to those reporting 7 hours of sleep per night (Table 2; hazard ratios [HRs]) (95% CI, 1.27[1.14–1.41] for ≤ 6 hours and 1.43[1.32–1.54] for ≥ 10 hours). These associations were attenuated with additional adjustment for age, gender, marital status, private health insurance, smoking status, alcohol consumption, body mass index, physical activity, and baseline health status. However, in the total sample short sleep (HR, 1.13[1.01–1.25]) and long sleep duration (HR, 1.26[1.16–1.36]) remained significantly associated with mortality risk compared to 7 hours of sleep.

Table 2. The relationship between sleep duration and mortality risk in the total sample. Data are presented as hazard ratios (with 95% confidence intervals) adjusted for covariates.

	N	IY	Events	Adjusted for age and gender		Fully adjusted results ^a	
				HR	95% CI	HR	95% CI
<6 h	8308	23,616	429	1.27*	1.14–1.41	1.13*	1.01–1.25
6 h	27,796	78,756	1016	1.03	0.96–1.11	0.99	0.91–1.06
7 h	54,335	153,205	1803	Referent		Referent	

	N	IY	Events	Adjusted for age and gender		Fully adjusted results ^a	
				HR	95% CI	HR	95% CI
8 h	92,789	258,233	3302	1.03	0.97–1.09	1.02	0.96–1.08
9 h	27,111	74,394	1088	1.05	0.97–1.13	1.04	0.96–1.12
P10 h	17,471	47,184	1144	1.43*	1.32–1.54	1.26*	1.16–1.36

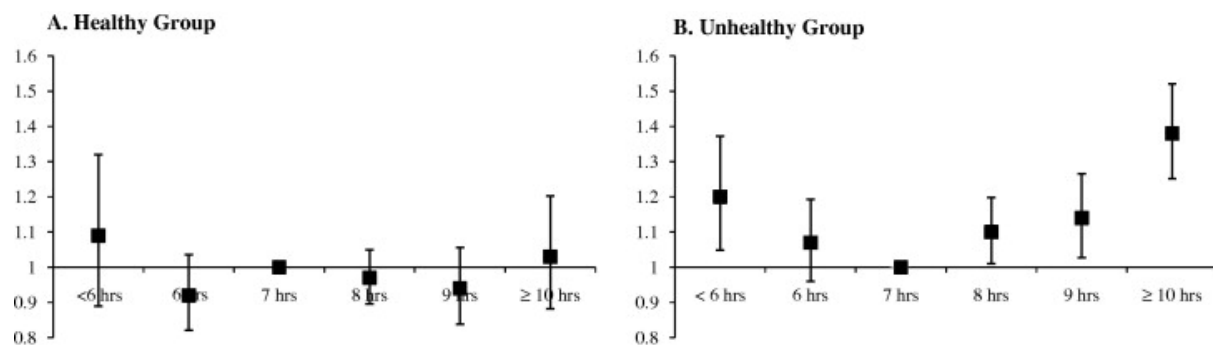
Abbreviations: CI, confidence interval; h, hour; HR, hazard ratio; IY, individual-years; N, number of participants.

* $p < 0.05$.

^a HR adjusted for age, gender, marital status, private health insurance, smoking status, alcohol consumption, body mass index, sufficient physical activity, and baseline health status.

When these relationships were separately examined in those classified as healthy at baseline, the association was attenuated such that there was no significant relationship of sleep duration to mortality (corresponding HRs, 1.09[0.89–1.32] and 1.03[0.88–1.20], respectively) (Fig. 1; Table 3). In contrast, a U-shaped relationship between sleep duration and mortality was observed in the less healthy group. The sleep duration by health status interaction was significant (for interaction, 12.69; $p = 0.026$), indicating that the relationship between sleep duration and mortality varied by baseline health status.

Figure 1. Mortality risk associated with each of the sleep categories for individuals in the healthy (A) and less healthy groups (B). Data are presented as hazard ratios (with 95% confidence intervals) adjusted for covariates. Although the hazard curves are separately shown in the figure, they were estimated from a single model based on the main effects for - and an interaction term between - health status and sleep duration.



DISCUSSION

In the present sample, and without comprehensive consideration of baseline health status, both short (< 6 hours) and long (≥ 10 hours) sleep were significantly associated with all-cause mortality, independent of a range of sociodemographic and behavioral factors. This finding is consistent with existing studies conducted in countries such as the United States, the United Kingdom, Finland, and Singapore [7], [8], [11] and [12]. However, further investigation indicated that the nature of this association significantly varied based on health status, which was assessed in relation to preexisting illness (e.g., cancer, heart disease) and functional limitation (determined using the Medical Outcomes Study Physical Functioning scale). In particular we found that short and long sleep duration were not associated with elevated mortality when data were restricted to individuals who were healthy at baseline. This group is least likely to have findings affected by residual confounding or reverse causality.

Table 3. Hazard ratios showing the association of sleep duration with mortality risk from a model including an interaction term between sleep duration and health status.

	N	IY	Events	HR	95% CI
<i>Healthy group</i> ^a					
<6 h	3252	9315	113	1.09	0.89–1.32

	N	IY	Events	HR	95% CI
6 h	15,585	44,521	432	0.92	0.83–1.04
7 h	35,884	101,451	1018	Referent	–
8 h	56,951	158,751	1564	0.97	0.89–1.05
9 h	14,597	40,040	408	0.94	0.83–1.05
P 10 h	5724	15,506	201	1.03	0.88–1.20
<i>Less healthy group^b</i>					
<6 h	5056	14,301	316	1.20 [*]	1.05–1.38
6 h	12,211	34,230	584	1.07	0.96–1.19
7 h	18,451	51,751	785	Referent	
8 h	35,839	99,478	1738	1.10 [*]	1.01–1.20
9 h	12,514	34,354	680	1.14 [*]	1.03–1.27
P 10 h	11,747	31,675	943	1.38 [*]	1.25–1.52

Abbreviations: CI, confidence interval; h, hour; HR, hazard ratio; IY, individual-years; N, number of participants.

* $p < 0.05$.

^a Group characterized by absence of cancer, heart disease, diabetes mellitus, and stroke, and method of scoring physical functioning (MOS-PF) score ≥ 75 .

^b Group characterized by the presence of one or more chronic conditions at baseline and a MOS-PF <75.

This finding is important, as a variety of mechanisms have been proposed to explain the relationship between sleep duration and mortality. It has been suggested, for example, that shorter sleep durations contribute to elevated mortality risk via pathways such as an increased risk for chronic health conditions including heart disease, diabetes mellitus, and obesity,

which have been linked with shorter sleep durations and overall mortality. Grandner and Drummond [13] also proposed that factors such as changes in cytokine levels and a reduced photoperiod (i.e., the rate of daylight to darkness) may contribute to elevated mortality in long sleepers.

Our results provide some evidence against these causal mechanisms and suggest that the relationship between sleep duration and mortality is due to residual confounding with poor health at baseline. This conclusion is based on the proposition that if sleep duration were genuinely causally related to mortality, then an association would be observed regardless of health status. Using data on the presence of specific chronic health conditions and functional limitations due to poor physical health or disability we were able to, a priori, define a group that was less likely to have substantial variations in sleep durations due to preexisting poor health. Because we did not observe an association between sleep duration and mortality in this specific group despite reasonable power, it suggests that residual confounding may underlie the relationship between sleep duration and mortality observed in the total sample.

Our findings are novel, as few studies have previously investigated if the association between sleep duration and mortality varies according to health status. Available studies indicate that short and long sleep generally are associated with mortality risk regardless of health status [1], [7], [8] and [10]. The exception has been shown in the study by Mesas et al. [1], who observed that the relationship between short sleep duration and mortality was only evident in individuals with poorer cognitive functioning. However, research investigating the relationship between insomnia and mortality risk also has indicated that this association is only evident in those with preexisting health conditions [22]. It is important to note that the assessment of health status has been relatively limited in previous studies examining sleep duration and mortality, with the focus primarily on preexisting disease. This is a limitation, as it is likely that sleep duration varies not only according to whether or not someone has a

specific illness (e.g., ischemic heart disease) but also according to the severity of the disease. This information is not appropriately captured by adjustment for binary variables reflecting health status (e.g., presence vs absence of a health condition). As a result, residual confounding may not have been effectively addressed in previous studies. Our research is better able to address this, as we assessed health status in relation to preexisting illness and functional limitations, which are more indicative of an individual's overall health. Therefore, our results provided supportive evidence that the nature of the association varies by health status and that residual confounding may well account for previous associations between sleep duration and mortality.

It is important to acknowledge that there are several ways to assess residual confounding. In addition to the approach adopted in our paper, another method involves investigating if the relationship between sleep duration and mortality changes with increasing duration of follow-up. If, for example, the magnitude of the relationship diminishes over time, then it suggests that the association is due to residual confounding with another factor at baseline. We were unable to perform these analyses in our study given that our analyses were limited to a relatively short period of follow-up. However, Cairns et al. [15] recently adopted this approach to investigate the relationship between daytime napping and the risk for cancer. Their results demonstrated that the magnitude of this relationship significantly weakened over time such that daytime napping was not associated with breast cancer and only marginally associated with other cancers 4 or more years after baseline. This finding suggests that the relationship between daytime napping and cancer risk also could be from preexisting disease. Therefore, although residual confounding can be difficult to investigate, it is something that needs to be carefully examined in the context of sleep duration and outcomes such as mortality. Two possible ways of investigating residual confounding in the present

context are to investigate the effects of preexisting health concerns and the effects of increased duration of follow-up.

Despite the novelty of the findings, there are several limitations of our study. Many large cohort studies use a single item to assess sleep duration, but this is potentially problematic as it may lead to inaccurate estimates of sleep duration and be biased by factors such as age. For example, self-reported sleep duration moderately correlates with actigraph-measured sleep but may overestimate sleep duration by up to 52 minutes a night [23]. Although this is a limitation of this study, the overestimation of sleep duration may bias the results towards the null. This hypothesis is supported by research showing that the magnitude of the U-shaped association between sleep duration and mortality is less pronounced when using subjective vs objective measures of sleep duration [23].

A further consideration is that sleep duration is just one dimension of sleep and does not provide an indication of sleep disturbances, which also may be important in understanding how sleep is related to mortality [24]. Future research should therefore assess other dimensions of sleep, such as sleep quality and sleep disturbances in addition to sleep duration. Our study included a range of factors that could potentially confound the association between sleep duration and mortality in addition to preexisting health. However, other factors such as obstructive sleep apnea and depression may also confound these relationships but were not included in our paper. Therefore, it is possible that the associations observed in the less healthy groups are the result of residual confounding due to these other factors. Future research may benefit from addressing these other variables as potential confounders to further clarify the nature of the relationship between sleep duration and mortality.

The period of follow-up in our study was relatively short, which can be a concern, as sleep is estimated to be relatively close to the event and also because the potential effects of sleep on mortality may take a longer period of time to occur. As noted above, longer periods of follow-up also could be beneficial in further investigating residual confounding.

A final limitation of our study relates to the response rate of 18%. Although this response rate is consistent with many contemporary cohort studies, it does raise the possibility of biases due to a lack of representativeness. In general, the 45 and Up Study is underrepresented by men, younger individuals, and those living in major cities [25]. In addition, the sample is wealthier and healthier (reflected by lower smoking rates and higher self-rated health) compared to the general population [25]. Empirical data from the 45 and Up Study support the general epidemiologic axiom that relative risks based on internal comparisons within the cohort are unlikely to be biased by lack of representativeness; however, the possibility of bias cannot be entirely excluded [25] and [26].

Conclusions

Despite these limitations, our study also has a lot of strengths including the use of longitudinal data from a large sample size. In addition, we were able to control for a large number of covariates (e.g., sociodemographic factors, health behaviors), which could have confounded the relationship between sleep duration and mortality. The utilization of a multidimensional measure to assess health, which combined preexisting health conditions with functional limitations to assess health status, also is a key strength of our study. This is because the combined measure incorporated both the presence and severity of a preexisting illness or health condition, and hence enabled us to better examine if residual confounding explained the relationship between sleep duration and mortality. This component is important, as sleep duration is increasingly discussed as a potential risk factor for mortality, but our results indicate that the nature of the relationship varies according to

health status and is not evident in individuals without health concerns and functional limitations at baseline. In combination with the known relationships of sleep disturbance to baseline health, the null findings of the sleep duration mortality in healthier individuals in our study suggest that the observed relationship of short and long sleep duration to mortality may well be a result of the preexisting disease.

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REFERENCES

1. Mesas AE, López-García E, León-Muñoz LM, Guallar-Castillón P, Rodríguez-Artalejo F. Sleep duration and mortality according to health status in older adults. *J Am Geriatr Soc* 2010;58:1870-7.
2. Amagai Y, Ishikawa S, Gotoh T, et al. Sleep Duration and Mortality in Japan: the Jichi Medical School Cohort Study. *J Epidemiol* 2004;14:124-28.
3. Heslop P, Smith GD, Metcalfe C, Macleod J, Hart C. Sleep duration and mortality: the effect of short or long sleep duration on cardiovascular and all-cause mortality in working men and women. *Sleep Med* 2003;3:305-14.
4. Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep and Mortality: A Population-Based 22-Year Follow-Up Study. *Sleep* 2007;30:1245-53.
5. Ikehara S, Iso H, Date C, et al. Association of Sleep Duration with Mortality from Cardiovascular Disease and Other Causes for Japanese Men and Women: the JACC Study. *Sleep* 2009;32:259 - 301.
6. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 2002;59:131-6.
7. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. *Sleep* 2004;27:440-4.
8. Shankar A, Koh W-P, Yuan J-M, Lee H-P, Yu MC. Sleep duration and coronary heart disease mortality among Chinese adults in Singapore: A population-based cohort study. *Am J Epidemiol* 2008;168:1367-73.

9. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. *Sleep* 2010;33:585-92.
10. Suzuki E, Yorifuji T, Ueshima K, et al. Sleep duration, sleep quality and cardiovascular disease mortality among the elderly: a population-based cohort study. *Prev Med* 2009;2-3:135-41.
11. Ferrie JE, Shipley MJ, Cappuccio FP, et al. A prospective study of change in sleep duration: Associations with mortality in the Whitehall II Cohort. *Sleep* 2007;30:1659-66.
12. Kronholm E, Laatikainen T, Peltonen M, Sippola R, Partonen T. Self-reported sleep duration, all-cause mortality, cardiovascular mortality and morbidity in Finland. *Sleep Med* 2011;12:215-21.
13. Grandner M, Drummond SP. Who are the long sleepers? Towards an understanding of the mortality relationship. *Sleep Med Rev* 2007;11:341-60.
14. Grandner M, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: the evidence, the possible mechanisms, and the future. *Sleep Med Rev* 2010;14:191-203.
15. Cairns BJ, Travis RC, Wang X-S, Reeves GK, Green J, Beral V. A short-term increase in cancer risk associated with daytime napping is likely to reflect pre-clinical disease: prospective cohort study. *Br J Cancer* 2012;107:527-30.
16. Kakizaki M, Kuriyama S, Nakaya N, Sone T, Nagai M, Sugawara Y, et al. Long sleep duration and cause-specific mortality according to physical function and self-rated health: The Ohsaki Cohort Study. *J Sleep Res* in press.

17. Banks E, Jorm L, Lujic S, Rogers K. Health, ageing and private health insurance: baseline results from the 45 and Up Study cohort. *Aust N Z Health Policy* 2009;6:17.
18. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
19. Ware JE, Kosinski M, Gandek B. SF-36 Health Survey Manual & Interpretation Guide. Lincoln: RI: QualityMetric Incorporated; 1993, 2000.
20. Hayes RD, Sherbourne CD, Mazel RM. RAND: User's manual for the Medical Outcomes Study (MOS) core measures of Health-Related Quality of Life. Santa Monica: CA: RAND; 1995.
21. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC) July 2008. Canberra: Australian Bureau of Statistics; 2008.
22. Hublin C, Partinen M, Koskenvuo M, Kaprio J. Heritability and mortality risk of insomnia-related symptoms: A genetic epidemiologic study in a population-based twin cohort. *Sleep* 2011;34: 957 – 64.
23. Kripke DF, Langer RD, Elliot JA, Klauber MR, Rex KM. Mortality related to actigraphic long and short sleep. *Sleep Med* 2011;12:28-33.
24. Chandola T, Ferrie JE, Perski A, Akbaraly TN, Marmot MG. The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: a prospective study from the Whitehall II cohort. *Sleep* 2010;33:739-44.

25. Mealing NM, Banks E, Jorm LR, Steel DF, Clements MS, Rogers KD. Investigation of relative risk estimates from studies of the sample population with contrasting response rates and designs. *BMC Med Res Methodol* 2010;10:26.
26. Ponsonby, A-L, Dwyer T, Couper D. Is this finding relevant? Generalisation and epidemiology. *Aust N Z J Public Health* 1996; 20: 54 – 56.